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CITATION:

Lee, Young-A ...[et al]. Prefrontal cortical dopamine from an evolutionary perspective.. Neuroscience bulletin 2015, 31(2): 164-174

ISSUE DATE:

2015-04

URL:

http://hdl.handle.net/2433/202035

Prefrontal Cortical Dopamine in Evolutionary Perspective

Running title: Prefrontal Dopamine in Evolution

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Number of Pages: 31
Running Title: 32 characters
Abstract: 116 words
Text: 4,718 words
References: 91
Figures: 2
Tables: 0
Supplemental Information: 0

Keywords: Neurodevelopment; Neoteny; Psychiatric disorder; Stress; Animal model; Synaptic plasticity; Environmental adaptation

Abstract

In this article, we propose a hypothesis that the prefrontal cortex (PFC) may acquire neotenic development in consequence of mesocortical dopamine (DA) innervation, which in turn drives evolution of the PFC into the complex brain functional system. Accordingly, in the evolutionary perspective, decreased DA signaling in the PFC associated with such an adverse environmental condition as chronic stress may be considered as an environmental adaptation strategy. Psychiatric disorders such as schizophrenia and attention deficit/hyperactivity disorder may be also understood as environmental adaptation or a by-product of such process that has emerged through evolution in humans. To investigate the evolutionary perspective of DA signaling in the PFC, domestic animals such as canines may be an useful model.

1. Introduction

The prefrontal cortex (PFC) is one of the central brain regions that mediate higher cognitive and affective function [1, 2]. Extensive investigation have been made to unveil the neural network information processing mechanisms as well as genetic and molecular machineries underlying PFC function. The PFC is also suggested to be evolutionarily the latest part of the brain structure, and therefore its function plays the most important role in organizing human-specific behavioral traits [1, 3, 4]. Nonetheless, how the PFC had evolved into the complex system in humans has remained unclear.

Mesocortical dopamine (DA) projection into the PFC from the ventral tegmental area of the midbrain has been shown to be essential for PFC function (For extensive reviews on this issue, see the article by Seamans and Yang [5]). In this article, we propose a hypothesis that mesocortical DA projection into the PFC may be one of biological substrates involved in evolution of the PFC. Moreover, this evolutionary process may consequently result in emergence of psychiatric disorders such as schizophrenia and attention deficit/hyperactivity disorder (ADHD).

2. Mesocortical DA Regulation of PFC Development

DA innervation into the cortex is more restricted than those of serotonin (5HT) and norepinephrine (NE). NE and 5HT projections arising from the locus coeruleus and dorsal raphe, respectively, covers almost the entire cortex, from the frontal cortical area to the posterior parts including the visual cortex [6]. In contrast, DA projections are distributed primarily into the frontal cortex and temporal cortex, and other cortical parts are spared from its innervations [7].

Development and maturation process in the cortical areas where DA innervates

appears to be slower than the other cortical areas where no DA innervation presents. A human imaging study has shown that development of the frontal and temporal cortex continues to young adulthood, which is much slower than that of other cortical areas [8]. In accordance with it, DA receptor (both D1 and D2 receptors) expression is dynamically changing until early adulthood [9] at which maturation of the PFC coincides. Such PFC DA receptor expression dyamics may impact PFC development (e.g. delaying developmental process if DA signaling affect a developmental timing and rate). In addition, NMDA receptor has been also suggested to play an important role in neuronal development [10]. Recent studies have shown that DA receptor is functionally and physically [11, 12] coupled to NMDA receptor. Thus, lower DA receptor expression during early development could also influence NMDA receptor-dependent developmental process. Such observations provide an insight that there may be a relationship between delayed cortical development/maturation and DA projection into the cortex.

Several lines of evidence suggest that DA signaling may be able to influence PFC development. First, Lumbe and colleagues examined development of DA and 5HT projections into the PFC in non-human primates at different ages using immunohistological staining for density of fibers containing tyrosine hydroxylase (TH) and 5HT that appose onto PFC pyramidal neurons [13]. They found that DA projection was not fully matured up until early adulthood. In contrast, 5HT projection was already matured at the early developmental stage. This observation suggests that DA development is an important factor that may determine timing of PFC development and maturation. On the other hand, if delayed PFC development is an innate process independent of development of DA innervations, 5HT projection into the PFC is also

likely to exhibit a delayed developmental pattern similar to that of DA projection.

There are also studies that examined the effects of neonatal DA depletion by 6-hydroxydopamine injection into the PFC of rodents. A study by Kalsbeek and colleagues has reported that PFC pyramidal neurons in adults rats that had received neonatal DA depletion were smaller in neuronal size with shorter dendritic length [14]. Such morphological changes can be interpreted in two ways; one interpretation is that the morphology of matured PFC pyramidal neurons in adult animals that have developed without DA signaling resembles to that of immature neurons. The other interpretation is that such morphological changes may indicate atrophy from a fully matured form of neurons. However, this latter interpretation is unlikely, since DA depletion is given at a neonatal period even before proliferative growth of neurons takes place. In addition, the PFC volume in rats with neonatal DA depletion is even larger than that of normal rats [15], contradicted to the case of atrophy in which shrinkage of neurons and thereby smaller volume is expected to happen, although such enlargement of the volume may still be attributed by proliferation of glia cells, but neurons.

Decreased mesocortical DA transmission has been suggested in the pathophysiology of ADHD [16]. If DA signaling affects PFC development, alterations of PFC developmental speed is expected to be observed in ADHD children. A magnetic resonance imaging study with ADHD children by Shaw and colleagues [17] has revealed that development of the gray matter volume in the PFC of ADHD children was significantly delayed compared to non-diagnostic children. This finding further supports that DA may be a biological substrate that promotes PFC development.

There are several studies showing that DA and stimulation of DA receptors facilitate neuronal growth [18-20]. These studies utilized striatal neurons; therefore, such

molecular mechanisms of DA-dependent facilitation of neuronal growth may not necessarily be applicable to PFC neurons. However, these studies still supports that DA signaling is involved in regulation of neuronal development.

Collectively, evidence suggests that mesocortical DA may play an important role on PFC developmental process, particularly in regulation of timing and speed of development and maturation. Thus, the PFC may acquire delayed development and maturation in consequence of DA innervations, as DA innervations do not mature up until adulthood (Figure 1). On the other hand, the cortical areas where DA does not innervate develop and mature faster than the PFC. Indeed, this does not mean that DA is a sole determinant of developmental process of the PFC, and it is possible that other neurotransmitters may also be involved.

3. Neotenic PFC Development with DA Signaling

Based on the above evidence, we now propose a hypothesis that mesocortical DA signaling may be an important biological substrate for evolution of the PFC, being enabled by neotenic development.

Neoteny is retention of juvenile traits in adults, which is thought to be an important factor for evolution, as it provides greater flexibility to adapt environment by delaying development of organs into specific function [21]. Indeed, sexual maturation of humans, which takes approximately two decades, is much longer than those of any other animals.

Development and maturation of the PFC in terms of synaptic spine density on dendrites of pyramidal neurons have been shown to continue up until early adulthood in humans [22], non-human primates [23], and rodents [24]. A more recent study have

suggested that maturational process of the PFC could be even much longer than that, continuing up to the thirties in humans [25]. Therefore, neotenic development is one of the most characteristic features of the PFC. Such delayed development may enable for the PFC to evolve into the highly complex system to mediate an assortment of cognitive and affective function.

In order that this hypothesis can be established, intrinsic correlation between evolutionary and developmental processes is required. Indeed, it has been suggested that evolution and development have strong relationships, such that there is research field called evolutionary developmental biology or "evo-devo" [26]. One of the key concepts of evolutionary developmental biology is the heterochrony, which refers changes in developmental timing and speed of organisms including neoteny. Genetic (e.g. Hox gene) and morphological evidence supporting that such heterochonic processes had played critical roles in evolution have been reported [27-32].

4. Lower PFC DA Signaling as Environmental Adaptation Strategy in Evolution

Our hypothesis predicts that mesocortical DA signaling may play an important role on the neotenic development, and thereby evolution, of the PFC, especially when DA signaling becomes lower than usual level. In this regard, it is important to note that, although decreased DA signaling is usually considered deficient and abnormal in the conventional neuroscience perspective, it could be even advantageous in the evolutionary perspective. How could decreased DA signaling in the PFC, which has been shown to cause cognitive and affective dysfunction [5, 33], be advantageous?

Stress has been shown to alter DA release in the PFC in rodents and primates [34]. Although a brief, acute stress exposure temporarily increases DA release in the

PFC [35], more severe, chronic stress decreases basal tonic DA tone regardless of stress types (e.g. restraint [36] or cold [37]) in adult animals. Indeed, chronic stress effects on PFC DA release of adult brains may be still different from that of developing brains. For instance, the recent study by Giovanoli and colleagues [38] has reported that chronic stress given in adolescence affects 5HT, but not DA, in the PFC. This study gives a couple of additional insights into our hypothesis. First, this study examined brain tissue contents, but not release of DA and 5HT, in the PFC. No change in DA concentration in PFC tissue with stress suggests that chronic stress may affect the release mechanism, but not synthesis, of DA. In addition, in this study, the effects of chronic stress in adolescence was examined in adulthood, such that stress effects may not be persistent, but they are reversible and can be recovered after a certain period of time. Therefore, delayed PFC development with decreased DA release may be limited only during organisms are under chronic stress environments, and once such a situation goes away, developmental speed may return to the normal level. Finally, and most importantly, this study utilized variable stress procedure (5 different stressors for twice for 10 days). Stress-induced alterations are often different depending on environments that stress is generated. For instance, chronic restraint, but not unpredictable, stress has been shown to induce amygdala-dependent brain and behavioral changes [39]. This suggests that environments in which stress is generated may determine how stress-induced alterations take place, whereas stress (stress hormones) and some associated changes such as decreased DA release may be rather a signal or trigger to cause subsequent environment-dependent changes. The unpredictable stress procedure has been probably developed to be utilized in animal studies, given that animals exhibit certain extent of habituation against repeated exposure to identical stressors, such that

unpredictable stress is more convenient to experimental setting. However, it is important to note that it is uncommon in the real life situation (both in humans and animals) that stressful environments rapidly change on each day. In our hypothesis, adaptation process should take place under a particular environment that yields stress in organisms for a prolonged period of time. Therefore, even if stress exposure is sufficiently long, adaptation may not happen when environments required to be adapted are rapidly changing.

Many studies have been conducted to unveil "how" chronic stress decreases DA signaling in the PFC (i.e. Tinbergen's proximate view [40]), with which we have already known quite details of molecular and cellular mechanisms of this process [33]. In contrast, "why" DA signaling is decreased by chronic stress in the PFC (i.e. Timbergen's ultimate view [40]) has not been explored to date. However, there must be a reason that DA signaling in the PFC has to be decreased by chronic stress.

Rodents and primates are estimated to be diverged around 100 million years ago in evolution [41]. Given that chronic stress induces similar, if not identical, cognitive and affective deficits as well as associated brain changes such as decreased DA signaling both in rodents and primates, these "disadvantageous" phenotypes were already present in mammalian organisms before divergence into rodents and primates, and have been maintained over 100 million years. Darwinian evolutionary (natural selection) theory [42] suggests that, if decreased DA signaling in the PFC and consequent alterations in PFC-dependent cognitive and affective processes by chronic stress is disadvantageous for survival of species, such phenotypes must have been vanished. Alternately, Lamarckian evolutionary (acquired inheritance of characteristics) theory [43] suggests that such stress-induced alterations have been evolved to as advantageous

environmental adaptation. In either way of evolutionary theories, therefore, decreased DA signaling and altered PFC function have been shown to produce major disadvantages in the normal environment, but such phenotypes may still be able to yield advantages for survival of species in such special environments that give chronic stress to organisms.

If decreased DA release delays PFC development, then chronic stress during development should also delay PFC maturation. There is no direct evidence to answer this question, and further investigation has been awaiting to be conducted in future. However, there are studies reporting that children who have had stress with family problems are found to exhibit delayed physical [44] and mental [45] development, indirectly supporting our hypothesis.

If chronic stress and associated brain changes play a role in evolution of the brain, such stress-induced alterations of brain function should be also inheritable. A brief report of Lamarckian-like, transgenerational inheritance of stress-induced alterations can be found in 1970 [46]. However, such study has been largely ignored until recently at which trasgnerational inheritance of epigenetic changes have been reported. Behavioral alterations caused by neonatal [47] or adult [48] exposure to stress have been recently reported again, confirming that stress-induced changes are inheritable. It appears that inheritance of these environmentally-induced (or acquired) phenotype involves epigenetic mechanisms [47, 48]. Since these studies have examined inheritance of stress-induced changes across two or three generations at most, it is still unclear whether such stress-induced epigenetic changes can be translated into equivalent genetic changes, or it is not necessary to be translated into genetic changes for inheritance of much longer generations. Nevertheless, domestication processes in

chicken [49] and silkworm [50] have been reported to involve epigentetic inheritance. Importantly, these studies raise a question why stress-induced changes, which is thought to be "deficits" and therefore disadvantageous phenotypes, have to be inherited and the biological mechanisms mediating them are still equipped in organisms.

Taken together, chronic stress could be driving force for PFC evolution, and chronic stress-induced decrease of DA signaling may provide greater flexibility to the PFC for being developed into the more complex system with neotenic development to adapt or overcome against severe environmental condition (Figure 2a, b).

5. Psychiatric Disorders Associated with Lower PFC DA Signaling

Decreased PFC DA release have been implicated in a psychiatric disorders such as ADHD [51] and schizophrenia [52]. The third implication based on our hypothesis is that such psychiatric disorders as schizophrenia and ADHD associated with PFC maldevelopment and decreased DA signaling may not necessarily be considered brain deficits, but could be rather understood as an environmental adaptation strategy (i.e. ADHD) or a by-product of adaptation (i.e. schizophrenia) that have emerged through evolution in humans.

5.1. ADHD

ADHD is one example of such a psychiatric condition that could illustrate the beneficial effects of decreased DA signaling in the PFC. ADHD is a childhood onset psychiatric condition with the core symptoms consisting of hyperactivity, impulsivity, and attention deficit (shorter attention span). These behaviors have been shown to be associated with decreased DA release in the PFC in animal studies [53-55]. Although these

symptoms are problematic in the modern human society such as school life, and therefore have to be treated, these symptoms still yield clear advantages for survival of species in a severe stressful environmental condition where life-threatening danger is approaching [56]. Hyperactivity enables constant exploration of the environment for faster detection of threats. Similarly, attention deficit with inability to sustain attention to a particular target enables shifting of attention and scanning from one object to another to monitor threats. Impulsivity also makes fast response to escape form dangers.

How delayed maturation with decreased DA signaling in the PFC may be associated with ADHD is still unclear. For instance, for animals living in the wild environment, faster maturation appears to be advantageous to escape from predators. Nevertheless, ADHD-like behavioral changes with decreased DA release in the PFC can be considered as a trade-off mechanism, such that delayed maturation causes animals more dangers, but ADHD-like behavioral changes reduces them.

5.2. Schizophrenia

Hypo-DA function in the PFC have been suggested in schizophrenia [52]. In addition, stress appears to be an important factor in schizophrenia, such that stress exposure often precedes onset of a first episode of symptoms as well as exacerbates or precipitates symptoms in patients [57, 58].

Various environmental and social conditions can be sources of stress. In the conventional view, environmental and social enrichments are usually considered beneficial, whereas poor environments and social isolation are deficient, for organisms. However, it is important to note that exaggerated environmental and social enrichments

can be also stressful. For instances, people living in urban cities, where greater environmental complexities exist than rural areas, are exposed to stronger stress than those living in rural areas [59]. Commuters during rush hours in the metropolitan cities also yield high intensity stress [60]. Therefore, social crowdedness within a group can be stressful to organisms. Stress with such exceeding social crowdedness is particularly interesting, since it can be evolutionary pressure to cope with such a stressful condition, with development of an adaptation strategy to make better assessment of behaviors or mental states of others, i.e. theory of mind (ToM) [61, 62]. Indeed, PFC activity has been shown to be associated with ToM [63]. Mirror neurons, which are a set of specialized neurons that become active in both motor action and observation of motor action demonstrated by others, are found in the PFC [64]. The mirror neuron circuit consisting with PFC and DA release in this region plays an important role in understanding behavior and emotional states of others [65]. Therefore, one scenario is that stress with over-crowdedness of a tribe may cause decreased DA release in the PFC, which is a signal or trigger to develop a strategy, ToM, as adaptation to this specific stressful environment through evolution.

In this process, decreased DA may be just a signal or trigger for adaptation by delaying development, and thereby providing greater adaptation period. Therefore, delayed development by itself also does not yield specific adaptation. How adaptation take places is dependent on a specific environment, such that adaptation could be as many changes as stressful environments that organisms are required to adapt differ. Indeed, stress is associated with various environmental factors (social isolation, social crowdedness, social defeat, physical pain, restraint, etc.), such that adaptation to stressful environments is not just only one change, but can be as many changes as

stressful environments are different. How the system changes for adaptation is dependent on types of stressors. Therefore, adaptation to stressful environments can vary, and psychiatric conditions emerged from such adaptation processes can be also variable and different. Evolution of such adaptation strategy is also unlikely achieved by just one generation, and most likely needs multiple generations. Thus, this argument does not imply that organisms with decreased PFC DA release immediately develop advantageous strategies including ToM as adaptive responses to stressful environments.

ToM deficits have been reported in schizophrenia [66, 67] and autism [61]. Nevertheless, the bases of ToM deficits may be different between these disorders. Crespi and Badcock have suggested that schizophrenia and autism may be diametrical psychiatric conditions, with autism associated with underdeveloped ToM, whereas schizophrenia associated with overdeveloped ToM [68]. Overdeveloped ToM can passably explain positive symptoms of schizophrenia such as paranoia and delusion. Schizophrenia patients often claim that they are controlled by TV, or neighbors are spying on them. These claims illustrate that patients peculiarly find an inorganic object having a mind like a living organism, or distortedly misunderstand other's mental state.

Collectively, one speculation may be able to be withdrawn. A part of schizophrenia symptoms may emerge as a by-product of the evolutionary process of ToM function as an adaptation strategy for stress associated with over-crowdedness within a group. This speculation is also consistent with the evolutionary psychiatric hypotheses proposed by Burns that schizophrenia may have emerged as a by-product in evolution of human social behavior [69], by Stevens and Price that schizophrenia may be

a phenotype of advantageous evolution for the role of splitting a group where population becomes too large [70], and by Saugstad that less clear cerebral lateralization observed in schizophrenia may be associated with late, slow maturation of the cortex [71]. On the other hand, social isolation can be also stressful, which could be also evolutionary pressure for an adaptation strategy against the isolated condition. Such evolutionary pressure may also be a basis of an autistic phenotype.

6. Predictions and Experimental Approaches

6.1. Predictions based on the hypothesis

Our hypothesis suggests that cortical areas such as the visual cortex where DA does not innervate develop and mature faster than cortical areas such as the PFC where DA innervates, since mesocortical DA signaling is involved in neuronal development of PFC neuronal network, but the mesocortical DA system does not mature up until adulthood. Development of the PFC consequently persists up until adulthood at which the mesocortical DA system also matures. Our hypothesis therefore predicts that PFC development and maturation are accelerated with augmentation of mesocortical DA signaling (e.g. pharmacological treatments such as psychostimulants. In contrast, PFC development and maturation are extraordinally delayed with attenuation of mesocortical DA signaling (e.g. pathological changes suggested in ADHD delay development of the PFC [17] or DA fiber depletion by 6-OHDA).

Such a prediction appears to be partly supported by recent studies suggesting that addictive drugs that increase DA release may accelerate aging [72-77]. These studies have shown that chronic abusers of amphetamine, cocaine, and alcohol exhibit cognitive decline and greater cortical atrophy indicative of accelerated aging. The study by

Cheng and colleagues has reported that heroin abusers exhibit lower telomerase activity, which results in shorter telomere, the biological marker of aging. Moreover, such lower telomerase activity is correlated with PFC gray and white matter thickness in abusers [78]. A possibility of accelerated aging by DA agonists is also interesting in relation to ADHD treatments in which DA agonists such as methylphenidate have been utilized. Given that ADHD may involve delayed development [17], the therapeutic effects of DA agonists in ADHD may be achieved not only by increased DA transmission, but also accelerating aging. Indeed, development and aging could be distinct processes, and therefore, the mechanisms involved in aging may not necessarily be similar to the mechanisms involved in neuronal development and maturation.

6.2. Empirical approach

Several experimental approaches may prove or disprove the hypothesis. There have been already many studies investigating the effects of physical, pharmacological, and psychological manipulations that alter PFC DA release on PFC function. However, very few studies have examined the impacts of these manipulations on PFC development. Thus, investigation focusing on alterations of developmental trajectory of PFC neural networks (timing and speed of synaptic growth and pruning, which could be measured by dendritic spine quantification [79] or expression of synapse-associated molecules such as synaptophysin [80]) caused by manipulations such as local DA depletion with microinfusion of 6-OHDA into the PFC, chronic exposure to stress (e.g. maternal deprivation [81]), and repeated psychostimulant administration, given at early stage of development in animals would be promising approaches to prove or disprove the hypothesis.

6.3. Domestic Animals: A Model of PFC Evolution with DA

An alternative approach for investigation of the evolutionary role of mesocortical DA in the PFC may be use of domestic animals.

Domestication is a process of selective breeding that consequently reduce aggression and facilitate prosociality in animals due to decreased pressure of intra- and inter-species competition for resources. Such domestication of animals is not necessarily achieved by human hands, but could be self-process among animals, i.e. self-domestication, that has been suggested to happen in bonobos [82]. In particular, domesticated animals exhibit neotenic features (delayed development, maintaining juvenile morphological features into adulthood) and higher cognitive function and prosociality, which are associated with PFC activity, than those of wild type animals [82]. In particular, domesticated animals include laboratory rodents (e.g. ICR mice, Sprague-Dawley rats), which are commonly used in biomedical research. it would be possible that PFC function and associated DA transmission in the PFC are significantly different between laboratory mice/rats and those in wild type rodents (e.g. MSM mice). Investigation for comparison between laboratory and wild type rodents for association between cognitive function and prosocial behavior and PFC neural network morphology, plasticity, volume, and DA level would be promising. In support of this approach, a recent study by Takahashi and colleagues has reported difference of social behavior between laboratory and wild type mice [83].

Use of canines as a model for understanding human social behavior has been proposed [84, 85]. The advantage of using canines as a model may become clearer as following. Individuals diagnosed with psychiatric disorders are considered as

abnormal in their social relationships partly because they are minority within population, and do not fit into the society that bases for the majority of (normal) individuals without phenotypes associated with disorders. A similar relationship can be applied between domestic and wild animals. In particular, social behavior of canines are quite distinct from those of wild animals. Such social behavior in canines that appear to be evolved as human companion may be considered as "abnormal" behavior from the view of wild animals.

Canines are also varied in their neotenic features. Some species such as Huskies and Corgis in adulthood are less neotenic appearance and look closer to the wild types such as Jackals and Coyotes, whereas other species such as Saint Bernard and Great Pyrenees exhibit stronger neotenic appearance with maintenance of juvenile-like appearance in adults [86]. In particular, neotenic appearance and cerebral DA level are correlated in canines [86, 87]. Thus, species close to the wild type and less neotenic appearance have higher cerebral DA level than those with greater neotenic appearance [86, 87], further supporting our hypothesis for the relationship between lower DA level and neoteny. Another advantage using canines for investigation is that canines have clear phylogeny, which enables to follow evolution of species relatively easily.

It is also interesting to note that unlike humans, "spontaneously occurring" neurological disorders such as Alzheimer's disease or Parkinson's disease are extremely rare, if there is any, in wild animals including non-human primates without artificial genetic or pharmacological manipulation. Canines are exception, which have spontaneously and endogenously occurring Alzheimer's disease-like alterations in their brains [88]. Although such spontaneously occurring Alzheimer's-like disease in canines

is not necessarily related to neotenic development of the PFC with DA signaling, this example illustrates that canines have acquired the brain system that is closer to that of humans than other wild animals through evolution with domestication. Therefore, canines could be a good model to understand how evolutionary change pertains emergence of human-specific brain disorders [89].

7. Conclusion

We have proposed a hypothesis that mesocortical DA may have a specific role on development and evolution of the PFC.

Indeed, there are several limitations in our hypothesis. For instance, DA transmission in the PFC is under regulation of brain areas such as limbic structures [90] and diencephalic nuclei including the habenula [91]. These limbic structures and other parts of the brain areas shown to regulate PFC DA release are relatively conserved areas across different species (i.e. evolutionarily old brain areas), suggesting that, although this possibility cannot be excluded, decreased DA level in the PFC may not be consequence of altered regulation mechanisms by other brain structures, but is more likely a result of an intrinsic change within the PFC selected through evolution. In addition, since our hypothesis is based on disorder models such as ADHD, schizophrenia, and chronic stress, a potential compromise is caused by the fact that these disorders involve brain mechanisms other than DA and PFC. However, this problem may be partly overcome by use of multiple disease models. Thus, each disorder involve various mechanisms, and difference of these multiple mechanisms may

create different conditions of disorders, although one of such mechanisms is common across the disorders (e.g. ADHD involves mechanisms A, B, C, whereas schizophrenia involves mechanisms A, D, E, chronic stress involves mechanisms A, C, F...). If the argument (i.e. role of DA in PFC development) is supported by all of these different conditions of disorders, then, the mechanism involved in this argument is most likely the one that is common across the disorders (i.e. DA change in the PFC), but not other mechanisms.

In conclusion, evolutionary perspective for understanding the role of neurochemical substances such as DA and its relation to brain disorders may open a new venue in neuroscience.

Acknowledgements

The authors are supported by Kyoto University, Ito Chubei Foundation, Ichiro Kanehara Foundation, and Institute of Life & Seizon.

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Figure Legends

Figure 1:

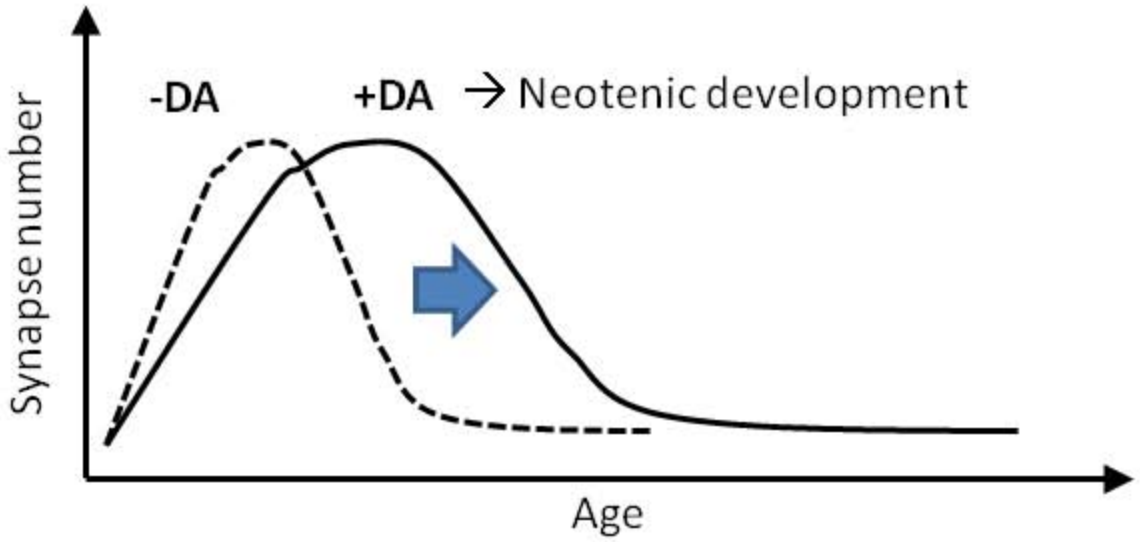
A schematic diagram illustrating delayed PFC development and maturation in terms of synaptogenesis and elimination of pyramidal neurons with mesocrotical DA signaling. In PFC pyramidal neurons, synapse number increases as growing. Then, during adolescence, synaptic elimination takes place to refine the neural network [22]. This process delays with DA innervations, as the DA system and DA innervations into the PFC continues up until adulthood.

Figure 2:

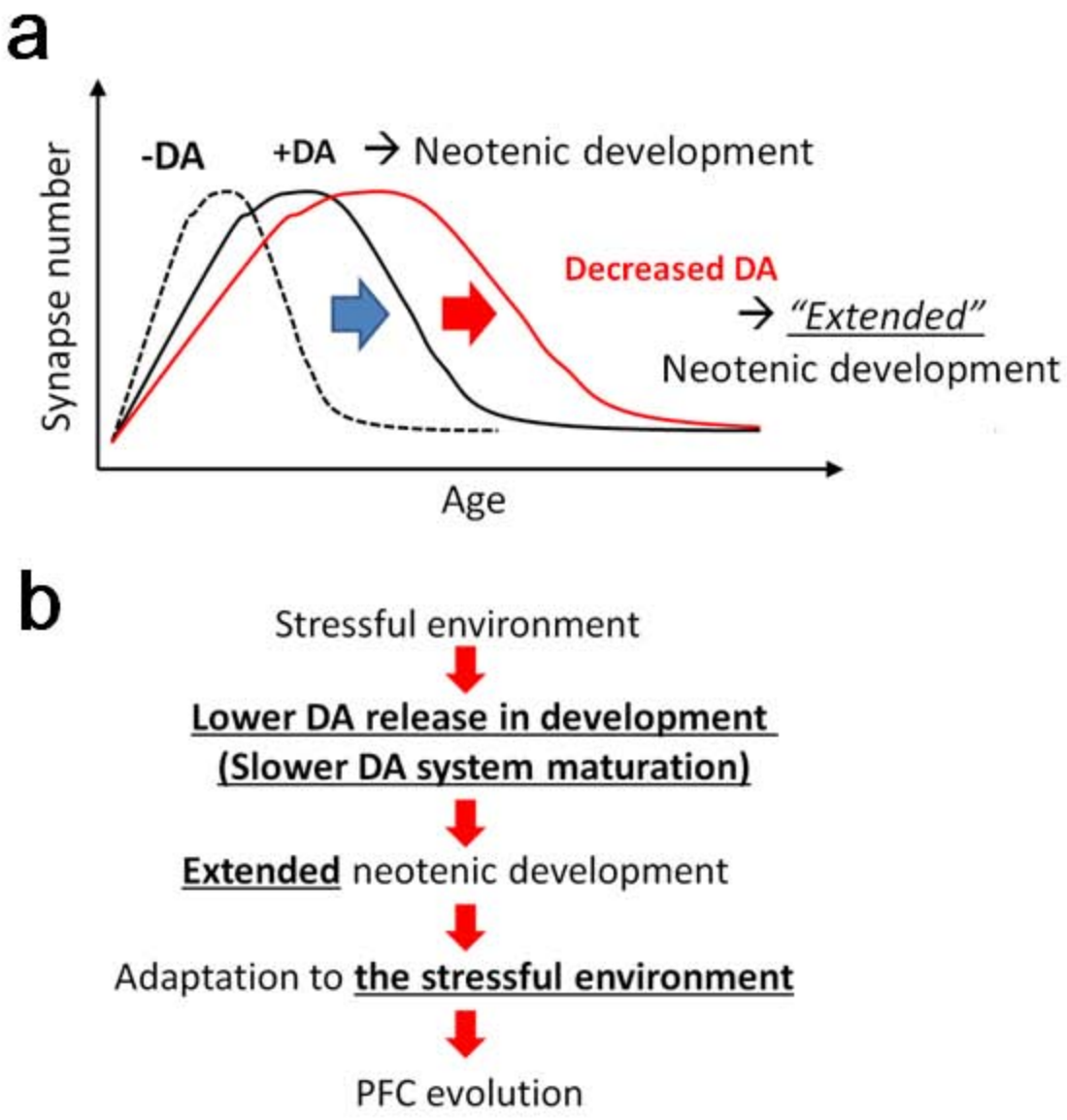
Diagrams illustrating the process that, in evolutionary perspective, lower mesocortical DA may play a beneficial role in the PFC.

(a) A schematic diagram illustrating extension of delayed PFC development and maturation expected to happen with lower DA signaling during developmental process.

(b) A schematic diagram illustrating the hypothetical evolutionary process of the PFC with mesocrotical DA signaling driven by severe, chronic stress.



Lee & Goto – Figure 1



Lee & Goto – Figure 2